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(54) Title: COMBINED METHOD FOR TREATING HORMONO-DEPENDENT DISORDERS

(57) Abstract: A method of preventing and treating estrogen dependent disorders selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, is disclosed which is comprised of administering to a mammalian patient in need of such treatment an effective amount of aromatase inactivator exemestane, alone or in combination with additional therapeutic agents.

COMBINED METHOD FOR TREATING HORMONO-DEPENDENT DISORDERS

FIELD OF THE INVENTION

The present invention relates to methods of preventing and treating hormono-dependent disorders, in particular, estrogen-dependent disorders, selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, benign breast disease and fibrocystic mastopathy, which comprises administering to a patient in need thereof aromatase inactivator exemestane, alone or in combination with additional therapeutic agents.

BACKGROUND OF THE INVENTION

Endometriosis is a disease in which patches of endometrial tissue, which normally is found only in the uterine lining (endometrium), grow outside the uterus. The misplaced endometrial tissue commonly adheres to the ovaries and the ligaments that support the uterus as well as the peritoneal lining of the abdominal cavity. Because the misplaced endometrial tissue responds to the same hormones that the uterus responds to, it may bleed during the menstrual period, often causing cramps, pain, irritation, and the formation of scar tissue. Moreover, it has been demonstrated that endometriotic tissue expresses aromatase activity, not seen in normal endometrium.

Endometriosis is estimated to occur in about 10 to 15 percent of menstruating women between the ages of 25 to 44. As many as 25 to 50 percent of infertile women may have endometriosis, which can physically interfere with conception.

Considerable circumstantial and laboratory evidence suggests that endometriosis is an estrogen-dependent disease. The main source for circulating estrogens in the premenopausal women is the ovary, where androgens are converted to estrogens by the enzyme aromatase. It has been assumed that estrogens are delivered to endometriotic implants via circulation. However, it has been recently demonstrated that significant levels of aromatase activity and

mRNA are also present in the stromal component of the endometriotic tissue, whereas aromatase expression was either absent or barely detectable in the eutopic endometrium. In addition, prostaglandin (PG)E2, which is present in very high levels in endometriotic tissues, was found to be the most potent inducer of aromatase activity in endometriosis-derived stromal cells. The production of PGE2 in endometrial stromal cells, in turn, was demonstrated to be simulated by cytokines and estradiol via enhancement of cyclooxygenase-2 (COX-2) expression, the enzyme responsible for the synthesis of PGE2. Therefore, aberrant regulation of the aromatase enzyme in endometriotic tissues, which favor increased local level of estradiol, is possibly involved in the development and growth of endometriosis.

In general, the aims of treatment of a patient with endometriosis include elimination of the misplaced endometriotic tissue, relief of pain and induction of pregnancy. Current treatments include administration of drugs that suppress the activity of the ovaries and slow the growth of endometrial tissue, surgery to remove the misplaced endometriotic tissue, surgical removal or the uterus, fallopian tubes and/or ovaries, or combinations of those treatments. While drug treatments are less invasive than surgery, administration of drugs such as combination estrogen-progestin oral contraceptives, progestins, danazol, and gonadotropin-releasing hormone (GnRH) agonists (such as Buserelin) is accompanied by multiple unwanted side-effects associated with hormone modulation, including bleeding between periods, hot flushes, predisposition to osteoporosis and mood swings. Furthermore, as yet available drug treatment doesn't cure endometriosis; the disease usually returns after treatment is stopped.

Benign breast disease, or often called fibrocystic breast disease, appears to be dependent on ovarian steroids. See Jacquemier et al., Cancer, 49, 2534 (1982). Aromatase inhibitors have not been tried in this disease, but antiestrogens seem to be of benefit. See Ricciardi & Iannirubertо, Obstet. Gynecol., 54, 80 (1979).

Uterine fibroids, which appear in the reproductive years and regress after menopause, are the result of cellular proliferation and differentiation in the uterine tissue regulated by the ovarian

steroids. At present, treatment of a patient suffering from uterine fibroids include surgery and administration of GnRH agonists.

Polycystic ovarian disease is one of the most common causes of infertility in women. The disease appears to result from an abnormality in steroid metabolism, and the major form of therapy in this disease is the antiestrogen, clomiphene. See Yen, Clin. Endocrinol., 12, 177 (1980).

Fibrocystic mastopathy is a condition considered in the past to confer an increased risk for breast cancer. Reevaluation of the outcome of this disorder has concluded that the overall increased risk of 1.86 of developing breast cancer, estimated by pooling together many published series, was more likely due to the selection of patients than to the real malignant potential of the disease. The presence of proliferation with cell atypia on pathologic assessment, however, is associated with an increased risk for breast cancer, especially if the patient has a positive family history. Fibrocystic disease occurs more often among individuals 30 to 55 years of age, and is frequently identified by women as multiple, round lumps in one or both breasts. The mammographic patterns of multiple areas of fibrosis and cysts are typical, but represent a difficult background for evaluation of an underlying neoplasia.

It is the object of the present invention to provide a method for preventing and treating estrogen dependent disorders selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, said method being not as invasive as surgery and not characterized by the adverse side effects that accompany administration of drugs that suppress the activity of the ovaries.

SUMMARY OF THE INVENTION

A method of prevention and treatment of estrogen dependent disorders selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, is disclosed

which is comprised of administering to a mammalian patient in need of such treatment an effective amount of the aromatase inactivator exemestane, alone or in combination with additional therapeutic agents.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method of preventing and treating estrogen dependent disorders selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, which comprises administering to a mammal patient in need of such treatment an effective amount of exemestane, either alone or in combination with an additional therapeutic agents, thus achieving a therapeutic effect.

Therefore, the invention provides a method of preventing and treating an estrogen dependent disorder selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, in a mammal in need of such treatment, including humans, comprising administering to said mammal exemestane in amounts sufficient to achieve a therapeutically useful effect.

The invention also provides a method of preventing and treating an estrogen dependent disorder selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, in a mammal in need of such treatment, including humans, comprising administering simultaneously, separately or sequentially to said mammal exemestane and another therapeutic agent, in amounts and close in time sufficient to achieve a therapeutically useful effect.

A further object of the present invention is to provide the use of exemestane in the manufacture of a medicament for preventing and controlling an estrogen dependent disorder

selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy.

The present invention also provides the use of exemestane in the manufacture of a medicament for preventing and controlling an estrogen dependent disorder selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, in a patient undergoing a simultaneous, separate or sequential treatment with another therapeutic agent.

The invention also provides a product containing exemestane and another therapeutic agent as a combined preparation for simultaneous, separate or sequential use in preventing and controlling an estrogen dependent disorder selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy.

The combination preparation according to the invention can also include combination packs or compositions in which the constituents are placed side by side and can be administered simultaneously, separately of sequentially to one and the same human being. Accordingly, exemestane and the other therapeutic agent may be present within a single or distinct container.

Accordingly, the invention also provides kits or single packages containing the pharmaceutical compositions useful for the combination treatment of the estrogen dependent disorder discussed above. The kits or packages may also contain instructions to use the pharmaceutical compositions in accordance with the present invention.

The inventors of the present invention have also found that prevention and control of the above mentioned estrogen-dependent disorders by combined administration of a therapeutically effective amount of exemestane and a therapeutically effective amount of another therapeutic agent, can produce a therapeutic effect which is greater than that obtainable by single administration of a therapeutically effective amount of either sole exemestane or the sole "additional" therapeutic agent. Namely, such combined therapy provides a synergistic or superadditive therapeutic effect.

Most importantly, they have found that such newly obtained therapeutic effect is not paralleled by the toxic effects, otherwise caused by single administration of either therapeutically effective amounts of exemestane or, of the "additional" therapeutic agent.

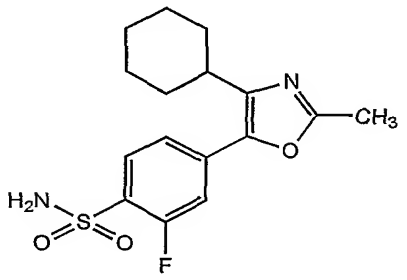
Product exemestane is compound 6-methylenandrost-1,4-diene-3,17-dione, which is known for instance from US Pat. No. 4,808,616.

The "additional" therapeutic agent for combination therapy with exemestane of the above mentioned estrogen-dependent disorders is for instance an agent selected from danazol, the class of COX-2 inhibitors, a non-steroidal anti-inflammatory compound (NSAID), a retinoid compound, a matrix metallo-protease inhibitor, an anti-estrogen, GnRH agonist or antagonist, a selective progestin receptor modulator (SPRM) and an angiogenesis inhibitor, or a mixture thereof.

A therapeutic agent mixture, according to the invention, which can be administered in combination with exemestane can comprise: one or more, preferably 2 to 4, in particular 2, therapeutic agents, as defined above.

Danazol, an androgen derivative which suppresses the pituitary-ovarian axis by inhibiting the release of GnRH, is well known in the art.

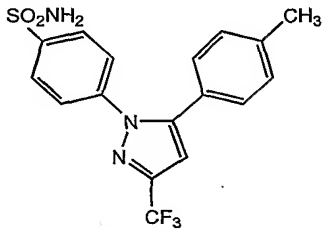
A COX-2 inhibitor, according to this invention is for instance a compound according to claims 34 to 41 of WO 00/38730. These compound are as follows:



JTE-522 (4-(4-cyclohexyl-2-methyloxazol-5-yl) -2-fluorobenzenesulfonamide),

5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl) pyridine,

2-(3, 5-difluorophenyl)-3-4(methylsulfonyl)phenyl)-2-cyclopenten-1-one,



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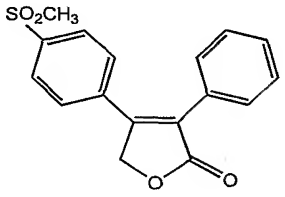
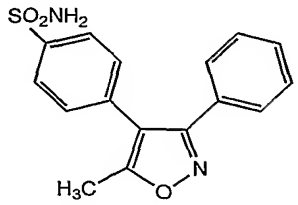


rofecoxib, (4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone),



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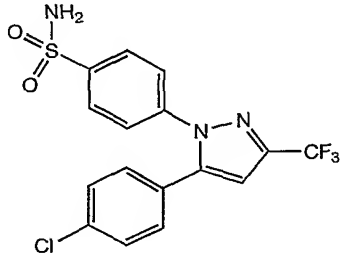
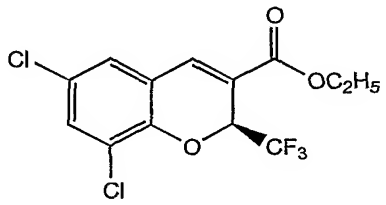
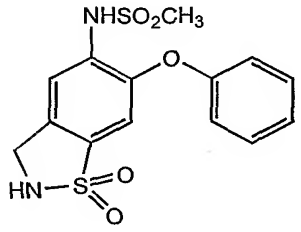
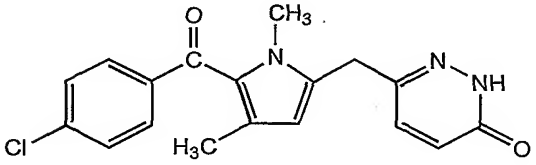


4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl] benzenesulfonamide,

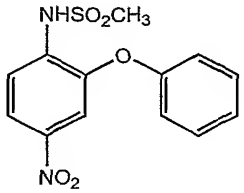




N-(2, 3-dihydro-1, 1-dioxido-6-phenoxy-1, 2-benzisothiazol-5-yl) methanesulfonamide,



6-[[5-(4-chlorobenzoyl)-1, 4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone,



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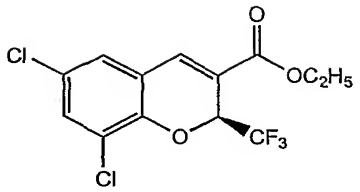

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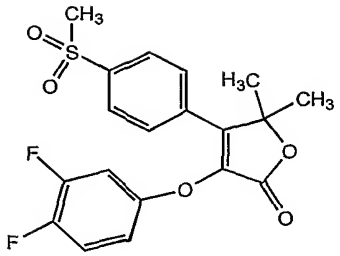

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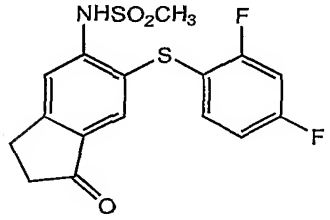

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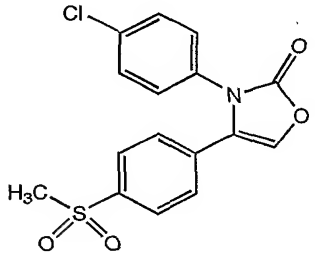
N-[6-[(2, 4-difluorophenyl) thio]-2, 3-dihydro-1-oxo-1H-inden-5-yl] methanesulfonamide,



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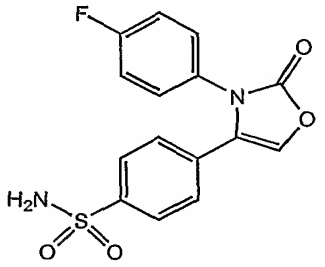
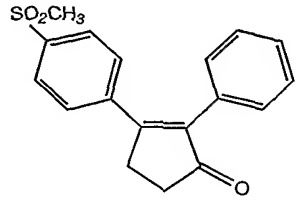


4-[3-(4-fluorophenyl)-2, 3-dihydro-2-oxo-4-oxazolyl] benzenesulfonamide,



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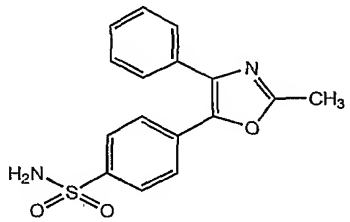

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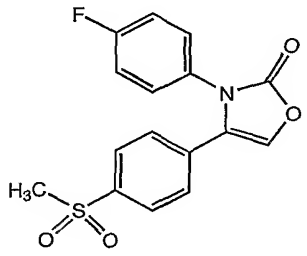

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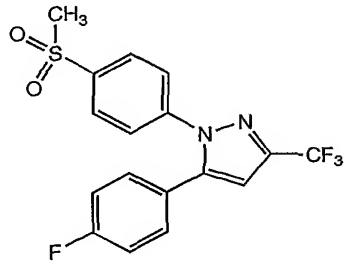

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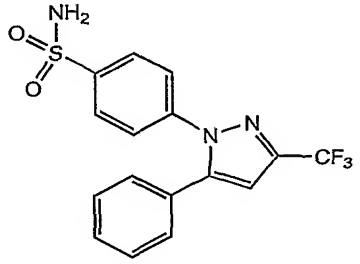

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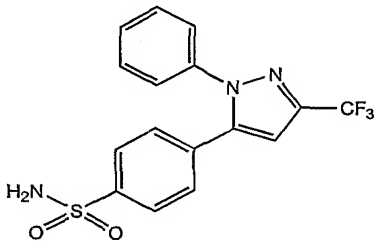

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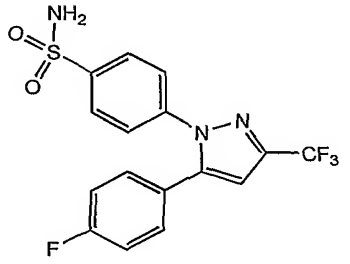

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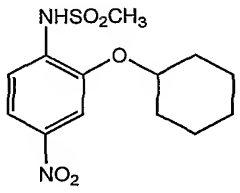

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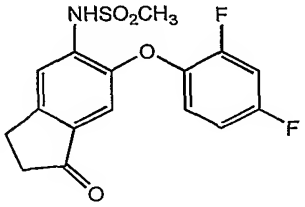

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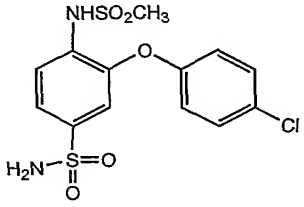

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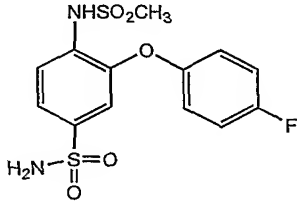

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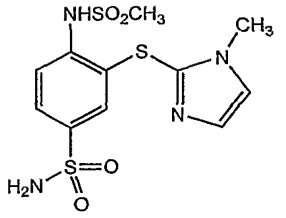
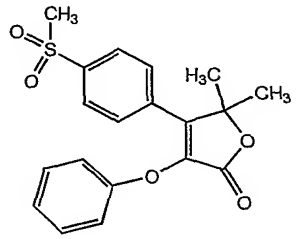
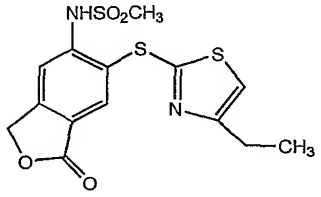


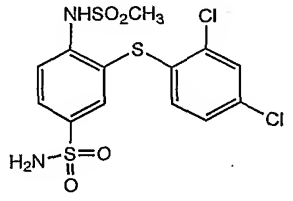
3-[(1-methyl-1H-imidzaol-2-yl)thio]-4 [(methylsulfonyl) amino] benzenesulfonamide,



5, 5-dimethyl-4-[4-(methylsulfonyl) phenyl]-3-phenoxy-2(5H)-furanone,



N-[6-[(4-ethyl-2-thiazolyl)thio]-1, 3-dihydro-1-oxo-5-isobenzofuranyl] methanesulfonamide,



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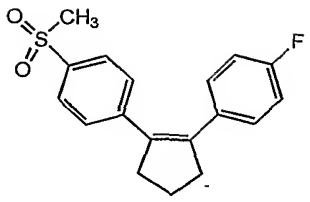
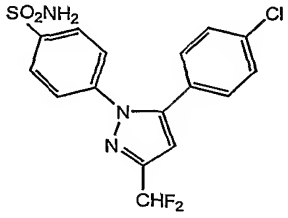
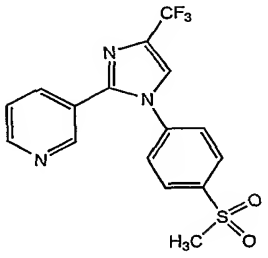


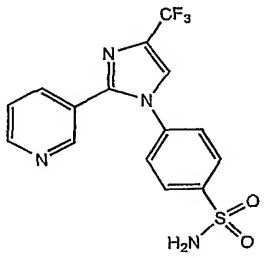
1-fluoro-4-[2-[4-(methylsulfonyl) phenyl] cyclopenten-1-yl] benzene,



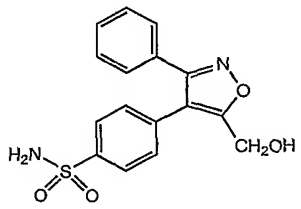
4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide,



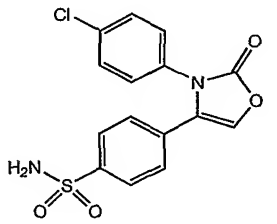
3-[1-[4-(methylsulfonyl) phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl] pyridine,



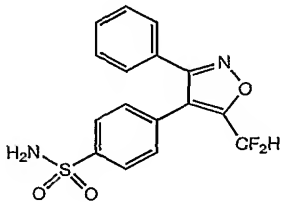
4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide,



4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl] benzenesulfonamide,



4-[3-(4-chlorophenyl)-2, 3-dihydro-2-oxo-4-oxazolyl] benzenesulfonamide,



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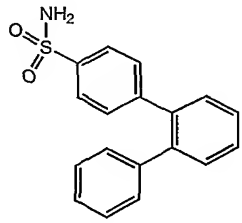
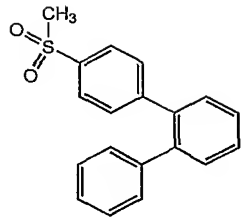
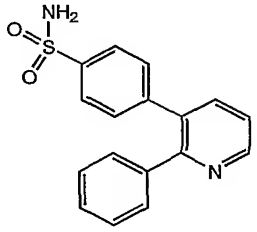


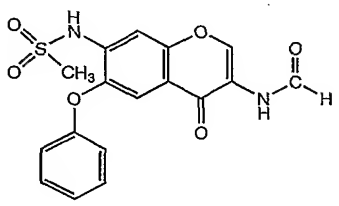
[1, 1':2', 1"-terphenyl]-4-sulfonamide,



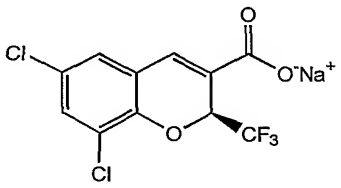
4-(methylsulfonyl)-1, 1', 2], 1"-terpheynyl,

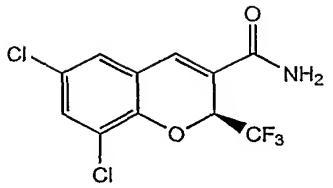


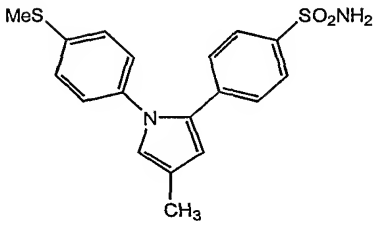
4-(2-phenyl-3-pyridinyl) benzenesulfonamide,

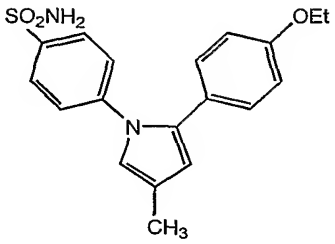


N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide,









Preferred examples of COX-2 inhibitors are compound T 614 (Toyama), darbufelone (Parke-Davis), compound L745337 (Merck Frosst), celecoxib, compound CT3 (Channel Terapeutics), rofecoxib, compound L783003 (Merck & Co.), compound JT3 522 (Japan Tobacco), compound 754 (Phytochemindo Reska), parecoxib, compound S2474 (Shianogi), compound LAS 33815 (Almirall-Prodesfarma), valdecoxib and compound MK 663 (Merck & Co.). More preferably celecoxib, rofecoxib, parecoxib and valdecoxib, in particular celecoxib.

A non-steroidal anti-inflammatory compound (NSAID), according to the invention, is e.g. a compound selected from acetyl salicylic acid, indometacin, sulindac, phenylbutazone, diclofenac, fentiazac, ketorolac, piroxicam, tenoxicam, mecoxicam, meloxicam, cinnoxicam, ibufenac, ibuprofen, naproxen, ketoprofen, nabumetone, niflumic acid and nimesulide, or a pharmaceutically acceptable salt thereof. Preferred NSAIDs are diclofenac, piroxicam,

tenoxicam, mecoxicam, meloxicam, ibufenac, ibuprofen, naproxen and ketoprofen, or a pharmaceutically acceptable salt thereof.

Examples of retinoid compounds according to the invention include, for example, Accutane; Adapalene; Allergan AGN-193174; Allergan AGN-193676; Allergan AGN-193836; Allergan AGN-193109; Aronex AR-623; BMS-181162; Galderma CD-437; Eisai ER-34617; Etrinate; Fenretinide; Ligand LGD-1550; lexacalcitol; Maxia Pharmaceuticals MX-781; mofarotene; Molecular Design MDI-101; Molecular Design MDI-301; Molecular Design MDI-403; Motretinide; Eisai 4-(2-[5-(4-methyl-7-ethylbenzofuran-2-yl)pyrrolyl])benzoic acid; Johnson & Johnson N-[4-[2-thyl-1-(1H-imidazol-1-yl)butyl]phenyl]-2-benzothiazolamine;Soriatane; Roche SR-11262; Tocoretinate; Advanced Polymer Systems trans-retinoic acid; UAB Research Foundation UAB-8; Tazorac; TopiCare; Taiho TAC-101; and Vesanoid.

Examples of matrix metallo-protease inhibitors according to the invention include known:
1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;
N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;
N-hydroxy-1-(pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;
N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-benzamide;
N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;
N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;
N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;
British Biotech BB-2516 (marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]-propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, [2S-[N4(R*), 2R*, 3S*]]-);

BMS 275291 disclosed in WO 97/19075;

Bayer Ag Bay-12-9566 (tanomastat), 4-[(4'-chloro[1,1-diphenyl]-4-yl)oxy]-2-[(phenylthio)methyl]butanoic acid;

Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2'-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-3-thiomorpholinecarboxamide;

CollaGenex Pharmaceuticals CMT-3 (metastat), 6-demethyl-6-deoxy-4-dedimethylaminotetracycline, batimastat (BB-94); and

Chiroscience D-2163, 2-[1S-([(2R,S)-acetylmercapto-5-phthalimido]pentanoyl-L-leucyl)amino-3-methylbutyl]imidazole.

An anti-estrogen, e.g. a selective estrogen receptor modulator (SERM), is preferably a SERM devoid of uterotrophic activity. Examples of SERMs, according to the invention, are tamoxifen, toremifene, arzoxifene, idoxifene, EM 800, fulvestrant and droloxifene.

Examples of GnRH (LHRH) agonists according to the invention are, e.g., leuprorelin, deslorelin, triptorelin, buserelin, nafarelin, goserelin, avorelin, histerelin, compound PTL 03001 (5-oxo-L-propyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide) (Peptech), compound AN 207 (6-[N6-[5-[2-[1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-mehoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-(2,3-dihydro-1H-pyrrol-1-yl).alpha.-L-lyxo-hexopyranosyl]oxy]-2-naphthacenyl]-1,5-dioxopentyl]-D-lysine]-,(2S-cis)-) (ASTA Medica Inc.), compound AN 238 L-threoninamide, N-[5-[2-[(2S,4S)-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-(2,3-dihydro-1H-pyrrl-1-yl).alpha.-L-lyxo-hexopyranosyl]oxy]-2-naphthacenyl]-2-oxoethoxy]-1,5-dioxopentyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-cyclic (2.fwdarw.7)-disulfide (ASTA Medica Inc.) and compound SPD 424 (LHRH-hydrogel implant) (Shire Pharmaceuticals Group), or a pharmaceutically acceptable salt thereof.

Preferred examples are triptorelin, leuprorelin and goserelin, or a pharmaceutically acceptable salt thereof, in particular triptorelin or a pharmaceutically acceptable salt thereof, e.g. as triptorelin pamoate.

Examples of GnRH (LHRH) antagonists, according to the invention, are e.g. cetrorelix, abarelix, ramorelix, teverelix, ganirelix, compounds A 75998 (Acetyl-D-(2-naphthyl)alanyl-D-(4-chlorophenyl)alanyl-D-(3-pyridyl)alanyl-seryl-(N-methyl)tyrosyl-N6-(nicotinoyl)-D-lysyl-leucyl-N6-(isopropyl)lysyl-propyl-D-alaninamide) and A 84861 (Tetrahydrofuran-2-(S)-ylcarbonyl-glycyl-D-(2-naphthyl)alanyl-D-(4-cholro)phenylalanyl-D-(3-pyridyl)-alanyl-L-(N-methyl)tyrosyl-D-[N6-(3-pyridylcarbonyl)]lysyl-L-leucyl-L-(N6-isopropyl)lysyl-L-propyl-D-alanylamide)(Abbot Labs.), GnRH immunogen (Aphton Co.), compound T 98475 (Isopropyl 3-(N-benzyl-N-methylaminomethyl)-7-(2,6-difluorobenzyl)-4,7-dihydro-2-(4-isobutyrylaminophenyl)-4-oxothieno[2,3-*b*pyridine-5-carboxylate hydrochloride) (Takeda), and compound MI 1544 (Acetyl-D-tryptophyl-D-cyclopropyl-alanyl-D-tryptophyl-L-seryl-L-tyrosyl-D-lysyl-L-leucyl-L-arginyl-L-propyl-D-alaninamide), or a pharmaceutically acceptable salt thereof.

Preferred example is abarelix or a pharmaceutically acceptable salt thereof.

Examples of selective progestin receptor modulators (SPRMs), according to the invention, are e.g. dienogest or a pharmaceutically acceptable salt thereof.

An angiogenesis inhibitor is e.g. an $\alpha v\beta 3$ integrin inhibitor, a protein kinase inhibitor, angiostatin, platelet factor 4 (endostatin), a VEGF inhibitor or thalidomide.

Vascular endothelial growth factor (VEGF) inhibitors and telomerase inhibitors are well known in the art. For instance, compounds SU 5416 and SU 6668, cited herein, are also VEGF inhibitors.

Moreover known VEGF inhibitors or antagonists are agents which suppress angiogenesis by reducing binding of VEGF to cellular receptors, including but not limited to, for example blocking monoclonal antibodies against the growth factor (e.g. rhuMAbVEGF, Ryan et al., Toxicol Pathol 1999, 27:78-86), against the receptor (e.g. DC101 and derivatives, Witte et al., Cancer Metastasis Rev 1998, 17:155-61), soluble forms of VEGF receptors (e.g. soluble Flt, Aiello et al., Proc Natl Acad Sci U S A 1995, 92:10457-61), or compounds which directly

antagonise interactions between VEGF and cell surface receptors (e.g. Fairbrother et al., Biochemistry 1998, 37:17754-64).

A protein kinase inhibitor, according to the invention, is for instance a tyrosine kinase inhibitor, in particular compound SU6668, i.e. 3-[4-(2-carboxyethyl-3,5-dimethylpyrrol-2-yl)methylidenyl]-2-indolinone, and compound SU5416, i.e. 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl]-2-indolinone, which are known from WO 96/40116 and WO 99/61422.

Examples of *αvβ3 integrin inhibitors* are known:
Vitaxin antibody (Ixsys); Merck KgaA EMD-121974, cyclo[RGDF-N(Me)V-];
(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid;
(2S)-7-[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2-yl]methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
(bR)-b-[[[(3R)-2-oxo-3-[2-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)ethyl]1-1-pyrrolidinyl]acetyl]amino]-d-(1H-indol-3-yl)pentanoic acid; and
(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]-glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine (compound SD 7784).

Angiostatin, endostatin and thalidomide are well known in the art. Pharmaceutically acceptable salts of the compound mentioned herein are well known in the art.

PHARMACOLOGY

The therapeutic effect of exemestane, either alone or in combination with an additional therapeutic agent, in preventing and treating estrogen-dependent disorders, according to the invention, has been shown as an example in an animal model of endometriosis.
Intact adult female rats were used. Endometriosis was induced by autotransplantation of a section of endometrium to a site under the renal capsule. In nontreated rats, the endometrial

transplants grew progressively during the following 4 weeks. The effect of the aromatase inhibitor exemestane and the GnRH agonist triptorelin on the growth of the endometrial explants was studied by giving the compound alone or in combination for 4 weeks. Either exemestane, given intramuscularly once a week for 4 consecutive weeks, or triptorelin, given subcutaneously once weekly for 4 weeks, caused a dose-related decrease in the volume of the explant, measured in animals laparotomized one week after the fourth weekly drug dose. When the compounds were given in combination at marginally or intermediate effective doses, an additive or synergistic effect was observed.

Method and Administration

In effecting treatment of a patient in a therapy/prophylactic method according to the invention, exemestane and the other therapeutic agent can be administered in any form or mode which makes the compounds bioavailable in effective amounts, including oral and parenteral routes.

By the terms "controlling" and "treating" an estrogen dependent disorder, as used herein, is meant a method of achieving a therapeutically useful effect, in particular of curing such disorder.

The term "therapeutically useful effect", besides curing such disorders, also means giving relief from pain accompanying such disorders, in particular in patients suffering from endometriosis.

Accordingly the invention also provides a method for improving the endometriosis pain symptoms of dismenorrea, dyspareunia and pelvic pain, in a patient suffering from endometriosis comprising administering to said patient exemestane alone or with another therapeutic agent, in amounts and close in time sufficient to achieve a therapeutically useful effect.

The term "close in time" means that in the combined method of treatment according to the invention, exemestane may be administered simultaneously with a further therapeutic agent or the compounds may be administered sequentially, in either order, to achieve a therapeutic effect.

By the term "administered" or "administering" as used herein is meant any acceptable manner of administering a drug to a patient which is medically acceptable including parenteral and

oral administration.

By "parenteral" is meant intravenous, subcutaneous, intra-nasal, pulmonary, intradermal or intramuscular administration.

Oral administration includes administering exemestane of the constituents of the combined preparation in a suitable oral form such as, e.g., tablets, capsules, suspensions, solutions, emulsions, powders, syrups and the like.

The actual preferred method and order of administration of the combined preparations of the invention may vary according to, inter alia, the particular pharmaceutical formulation of exemestane being utilized, the particular pharmaceutical formulation of the other therapeutic being utilized, the particular estrogen-dependent disorder to be prevented or treated and the particular patient being treated.

In the combined method of prevention or treatment according to the subject invention, exemestane may be administered simultaneously with the other therapeutic agent or the compounds may be administered sequentially, in either order. Preferably the compounds are administered sequentially. In particular when the combination treatment comprises exemestane and a GnRH agonist or antagonist, preferably, the compounds are administered in such a way that in the patient both inhibition of hormone output of her ovaries and inhibition/inactivation of aromatase enzyme are contemporaneously provided, and thus a therapeutic useful effect is achieved.

Dosage

The dosage ranges for the administration of the combined preparation may vary with the age, condition and extent of the disease in the patient and can be determined by one of skill in the art.

The dosage regimen must therefore be tailored to the particular of the patient's conditions,

response and associate treatments in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

According to the method of preventing and treating estrogen dependent disorders in mammals, provided the present invention, exemestane for instance can be administered orally in a dosage range varying from about 2.5 mg daily to about 600 mg daily, in particular from about 10 to about 50, more preferably from about 10 to about 25 mg daily, or parenterally in a dosage ranging from about 50 to about 500 mg per injection.

As a preferred embodiment of the invention, exemestane may be orally administered in the form of a complex with cyclodextrins, in particular exemestane/β-cyclodextrin complex, at a daily dosage ranging from about 10 to about 20 mg, preferably about 15 or 20 mg.

The effective therapeutic amounts of the other therapeutic agents to be used in combination with exemestane, according to the invention, are in general those commonly used in therapy for such compounds. More specifically, a therapeutically effective amount of another therapeutic agent means an amount of a compound, which when administered in combination with exemestane, is effective to prevent or treat estrogen- dependent disorders, as herein defined.

Determination of a therapeutically effective amount is well within the capability of those skilled in the art.

For instance an effective amount of compound SU 5416 or SU 6668 is an amount in accordance with the teaching of WO 99/61422.

An effective amount of compound SD 7784 is from about 10 to about 300 mg/kg, preferably per os, in particular from about 20 to about 200 mg/kg.

An effective amount of thalidomide may be in the range of about 100 to about 400 mg/day.

An anti-estrogen can be administered in a dosage according to the common practice, e.g. in a dosage of about 0.1 to about 30 mg/Kg body weight per day.

An effective amount of tamoxifen may be in the range of about 10 to about 40 mg/day. An effective amount of fulvestrant may be in the range of about 50 mg to about 300mg/day i.m., in particular of about 100 to about 250 mg/day i.m.

An effective amount of raloxifen may be in the range of about 5 to about 350 mg/day, in particular about 60 mg/day.

An effective amount of a COX-2 inhibitor may be in the range of about 0.1 to about 2000 mg, preferably in the range of about 0.5 to about 500 and most preferably between about 1 and about 200 mg. In particular as to celecoxib, rofecoxib, parecoxib and valdecoxib, a daily dosage of about 0.01 to about 100 mg/Kg body weight, preferably between about 0.1 and about 50 mg/Kg body weight may be appropriate. The daily dosage can be administered in one to four doses per day.

More particularly, as to celecoxib a dosage from about 50 to about 500 mg, in particular about 200 mg, once or twice a day may be appropriate.

As to rofecoxib the dosage normally ranges from about 12.5 to about 50 mg/day. The route of administration is preferably systemic e.g. oral or parenteral, in particular intravenous or intramuscularly.

Therapeutic dosages for SPRMs range between 2 to 50 mg/day.

Therapeutic dosages for GnRH agonists/antagonists like leuprolide are administered i.m. in doses varying from 1.5 to 15 mg, preferrably around 3.75 mg per month or 12.75mg per 3 months.

Goserelin can be administered as goserelin acetate by subcutaneous administration of slow release goserelin at a dosage from about 3 to about 12 mg.

Triptorelin can be administered for instance as triptorelin pamaote by intramuscular administration of a sustained release formulation, in such a way that there is an interval from about 1 to 4 months between each administration and at a dosage from about 3 to about 20 mg. In particular triptorelin pamoate can be administered intramuscularly in the form of microparticles as described in US Pat. No. 5,225,205 and US Pat. No. 5,776,885, and more specifically as 1-month depot formulation 3.75 mg.

An effective amount of a NSAID, according to the invention is generally the one commonly used in therapy for such compound. For instance an effective amount of naproxen may be in the range of about 300 mg to about 750 mg once or twice a day.
An effective amount of piroxicam may be in the range of about 15 mg to about 50 mg once or twice a day.

An effective amount of acetyl salicylic acid may be in the range of about 150 to about 1000 mg once or twice a day.

According to a preferred feature of the invention it is here provided a method of treating and preventing an estrogen dependent disorder selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, in a mammal in need of such treatment, including humans, comprising administering simultaneously, separately or sequentially to said mammal exemestane and a COX-2 inhibitor selected from celecoxib, rofecoxib, parecoxib and valdecoxib, in particular celecoxib and rofecoxib, especially celecoxib, in amounts and close in time sufficient to produce a therapeutically useful effect.
According to a further preferred feature of the invention it is here provided the use of exemestane in the manufacture of a medicament for preventing or controlling an estrogen

dependent disorder selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, in a patient undergoing a simultaneous, separate or sequential treatment with a COX-2 inhibitor selected from celecoxib, rofecoxib, parecoxib and valdecoxib, in particular celecoxib and rofecoxib, especially celecoxib.

According to such preferred features exemestane is administered orally at about 25 mg/day and celecoxib is administered orally at a dosage of about 200 mg, one or twice a day.

According to a preferred feature of the invention it is here provided a method of treating and preventing an estrogen dependent disorder selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, in a mammal in need of such treatment, including humans, comprising administering simultaneously, separately or sequentially to said mammal exemestane and a GnRH agonist or antagonist selected from triptorelin, cetrorelix, and leuprolide, in particular triptorelin and leuprolide, in amounts and close in time sufficient to produce a therapeutically useful effect.

According to such preferred features exemestane is administered orally at about 25 mg/day; triptorelin and leuprolide one or every three months at a dose of about 3 or about 20 mg, respectively, in particular of about 3.75 or about 12.75 mg, respectively.

According to a further preferred feature of the invention it is here provided the use of exemestane in the manufacture of a medicament for preventing or controlling an estrogen dependent disorder selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, in a patient undergoing a simultaneous, separate or sequential treatment with a GnRH agonist or antagonist selected from triptorelin, cetrorelix, and leuprolide, in particular triptorelin and leuprolide more preferably triptorelin.

As an example a kit according to the present invention provides an exemestane 25 mg oral or 50-500 mg parenteral composition and a triptorelin depot formulation 3.75 mg.

A pharmaceutically composition containing exemestane and/or another therapeutic agent according to the invention can be prepared according to well known techniques to those skilled in the art.

A pharmaceutical composition for intramuscular administration containing triptorelin pamoate in the form of a depot formulation can be prepared for instance as described in US Pat. No. 5,225,205 and US Pat. No. 5,776,885.

A pharmaceutical composition containing exemestane can be prepared according to US Pat. No. 4,808,616. In particular an exemestane/β-cyclodextrin complex formulation can be obtained as follows:

Exemestane 20 mg Tablet

Composition:	exemestane	20.00 mg
	Beta-cyclodextrin	178.00 mg
	Avicel PH101	75.00 mg
	Explotab	24.00 mg
	Magnesium stearate	3.00 mg

According to methods well known in the art an exemestane/cyclodextrin kneaded system can be prepared.

All references cited in this disclosure are incorporated herein by reference.

CLAIMS

1. Use of exemestane in the manufacture of a medicament for preventing and controlling an estrogen dependent disorder selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy.

2. The use according to claim 1, wherein when administered orally the amount of exemestane in the medicament is from about 2.5 mg to about 600 mg daily.

3. The use according to claim 1, wherein when administered orally the amount of exemestane in the medicament is from about 10 mg to about 50 mg daily.

4. The use according to claim 1, wherein when administered orally the amount of exemestane, in the medicament is from about 10 mg to about 25 mg daily.

5. The use according to claim 1, wherein when administered parenterally the amount of exemestane in the medicament is from about 50 mg to about 500 mg.

6. Use of exemestane in the manufacture of a medicament for preventing and controlling an estrogen dependent disorder selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, in a patient undergoing a simultaneous, separate or sequential treatment with an additional therapeutic agent.

7. The use according to claim 6, wherein the additional therapeutic agent is selected from the group consisting of danazol, a COX-2 inhibitor, a non-steroidal anti-inflammatory compound (NSAID), a retinoid compound, a matrix metallo-protease inhibitor, an anti-estrogen, GnRH agonist or antagonist, a selective progestin receptor modulator (SPRM) and an angiogenesis inhibitor, or a mixture thereof.

8. The use according to claim 6, wherein the additional therapeutic agent is a mixture comprising from 2 to 4 agents selected from the group consisting of danazol, a COX-2 inhibitor, a non-steroidal anti-inflammatory compound (NSAID), a retinoid compound, a matrix metallo-protease inhibitor, an anti-estrogen, GnRH agonist or antagonist, a selective progestin receptor modulator (SPRM) and an angiogenesis inhibitor.

9. The use according to claim 7, wherein the COX-2 inhibitor is selected form the group consisting of celecoxib, rofecoxib, parecoxib and valdecoxib.

10. The use according to claim 7, wherein the COX-2 inhibitor is celecoxib.

11. The use according to claim 7, wherein the anti-estrogen is a SERM devoid of uterotrophic activity.

12. The use according to claim 7, wherein the SERM is selected from the group consisting of tamoxifen, toremifene, arzoxifene, idoxifene, EM 800, fulvestrant and droloxifene.

13. The use according to claim 7, wherein the GnRH agonist is selected from the group consisting of leuprorelin, dislorelin, triptorelin, buserelin, nafarelin, goserelin, avorelin, histerelin, compound PTL 03301, compound AN 207, compound TX 397, compound AN 201 and compound SPD 424, or a pharmaceutically acceptable salt thereof.

14. The use according to claim 7, wherein the GnRH agonist is selected from the group consisting of triptorelin, goserelin and leuprorelin or a pharmaceutically acceptable salt thereof.

15. The use according to claim 13, wherein the GnRH agonist is triptorelin pamoate.

16. The use according to claim 15, wherein the GnRH agonist triptorelin pamoate is in the form of a sustained release formulation, at a dosage from about 3 to about 20 mg.

17. The use according to claim 15, wherein the GnRH agonist triptorelin pamoate is in the from of 1 month depot formulation 3.75 mg.

18. The use according to claim 7, wherein the GnRH antagonist is selected from the group consisting of cetrorelix, abarelix, ramorelix, teverelix, ganirelix, compounds A 75998 and A 84861, compound PM-OV-92, GnRH immunogen, compound D 26344, compound T 98475 and compound MI 1544, or a pharmaceutically acceptable salt thereof.

19. The use according to claim 7, wherein the GnRH antagonist is abarelix or a pharmaceutically acceptable salt thereof.

20. The use according to claim 7, wherein the SPRM is dienogest or a pharmaceutically acceptable salt thereof.

21. A product containing exemestane and another therapeutic agent as a combined preparation for simultaneous, separate or sequential use in preventing and controlling an estrogen dependent disorder selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian diseas, fibrocystic breast disease and fibrocystic mastopathy.

22. A method of preventing and treating an estrogen dependent disorder selected from the group consisting of endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, in a mammal in need of such treatment, including humans, comprising administering to said mammal exemestane in amounts sufficient to achieve a therapeutically useful effect.

23. The method according to claim 22, wherein when administered orally the amount of exemestane is from about 2.5 mg to about 600 mg daily.

24. The method according to claim 22, wherein when administered orally the amount of exemestane is from about 10 mg to about 50 mg daily.

25. The method according to claim 22, wherein when administered orally the amount of exemestane is from about 10 mg to about 25 mg daily.

26. The method according to claim 22, wherein exemestane is administered in the form of exemestane/β-cyclodextrin complex at a daily dosage from about 10 mg to about 20 mg.

27. The method according to claim 22, wherein when administered parenterally the amount of exemestane is from about 50 mg to about 500 mg.

28. A method of preventing and treating an estrogen dependent disorder selected from endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycistic ovarian disease, fibrocystic breast disease and fibrocystic mastopathy, in a mammal in need of such treatment, including humans, comprising administering simultaneously, separately or sequentially to said mammal exemestane and another therapeutic agent, in amounts and close in time sufficient to achieve a therapeutically useful effect.

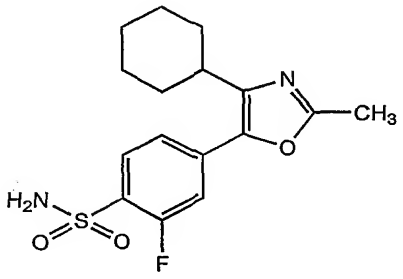
29. The method according to claim 28, wherein the additional therapeutic agent is selected from the group consisting of danazol, a COX-2 inhibitor, a non-steroidal anti-inflammatory compound (NSAID), a retinoid compound, a matrix metallo-protease inhibitor, an anti-estrogen, GnRH agonist or antagonist, a selective progestin receptor modulator (SPRM) and an angiogenesis inhibitor, or a mixture thereof.

30. The method according to claim 28, wherein a mixture of additional therapeutic agents, to be administered in combination with exemestane comprises from 2 to 4 agents selected from the group consisting of danazol, a COX-2 inhibitor, a non-steroidal anti-inflammatory compound (NSAID), a retinoid compound, a matrix metallo-protease inhibitor, an anti-

estrogen, GnRH agonist or antagonist, a selective progestin receptor modulator (SPRM) and an angiogenesis inhibitor.

31. The method according to claim 29, wherein the additional therapeutic agent is danazol.

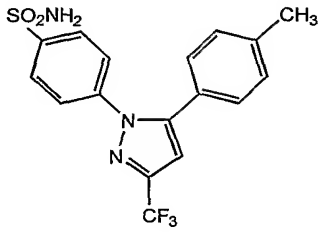
32. The method according to claim 29, wherein the COX-2 inhibitor is selected from the group consisting of:



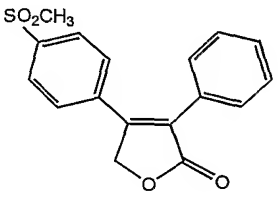
JTE-522 (4-(4-cyclohexyl-2-methyloxazol-5-yl) -2-fluorobenzenesulfonamide);

5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(methyl-5-pyridinyl) pyridine;

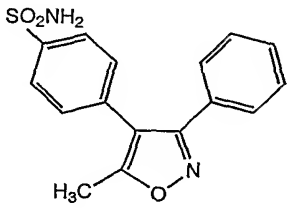
2-(3, 5-difluorophenyl)-3-4(methylsulfonyl)phenyl)-2-cyclopenten-1-one;



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide;

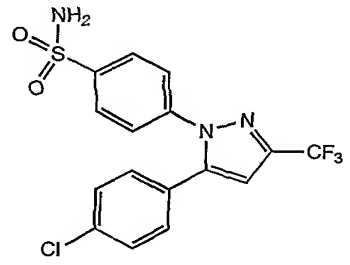


rofecoxib, (4-(4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone);

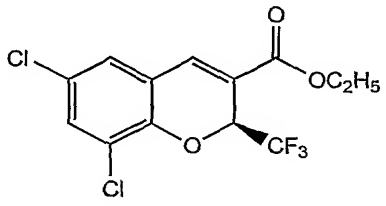


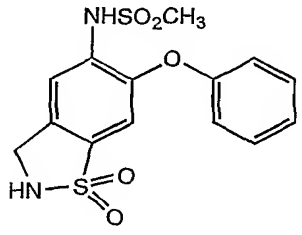
4-(5-methyl-3-phenylisoxazol-4-yl) benzenesulfonamide;

N-[[4-(5-methyl-3-phenylisoxazol-4yl] phenyl]sulfonyl] propanamide;

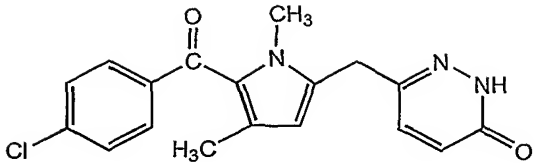


4-[5-(4-chorophenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl] benzenesulfonamide;

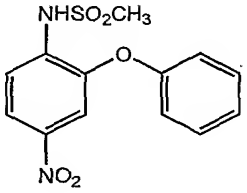




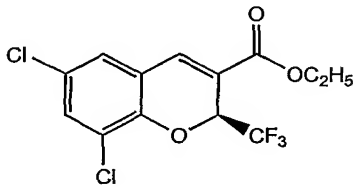
N-(2, 3-dihydro-1, 1-dioxido-6-phenoxy-1, 2-benzisothiazol-5-yl) methanesulfonamide;

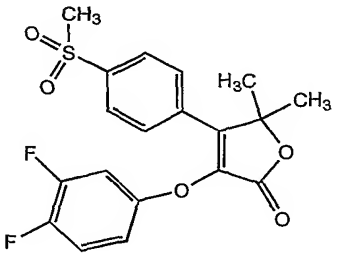


6-[[5-(4-chlorobenzoyl)-1, 4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone;

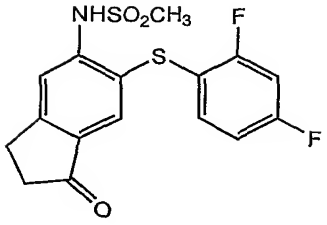


N-(4-nitro-2-phenoxyphenyl) methanesulfonamide;

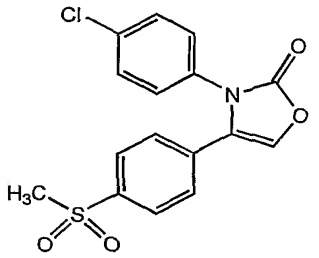




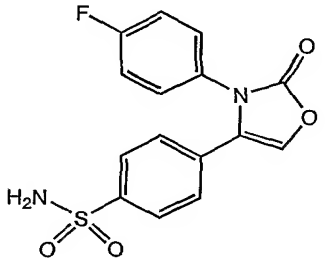
3-(3,4-difluorophenoxy)-5, 5-dimethyl-4-[4-(methylsulfonyl) phenyl]-2 (5H)-furanone;



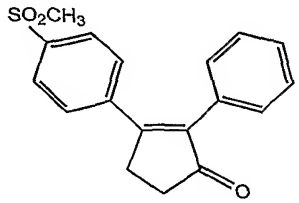
N-[6-[(2, 4-difluorophenyl) thio]-2, 3-dihydro-1-oxo-1H-inden-5-yl] methanesulfonamide;



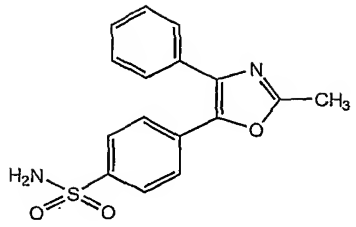
3-(4-chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-2 (3H)-oxazolone;



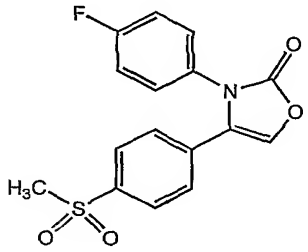
4-[3-(4-fluorophenyl)-2, 3-dihydro-2-oxo-4-oxazolyl] benzenesulfonamide;



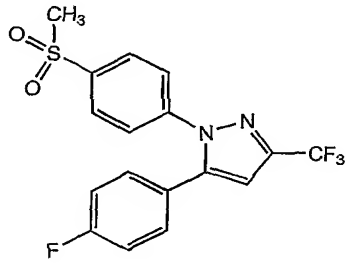
3-[4-(methylsulfonyl) phenyl]-2-phenyl-2-cyclopenten-1-one;



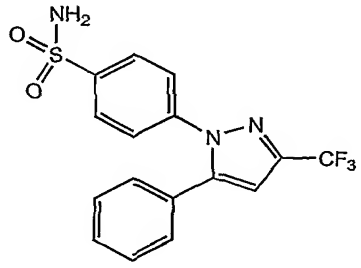
4-(2-methyl-4-phenyl-5-oxazolyl) benzenesulfonamide;



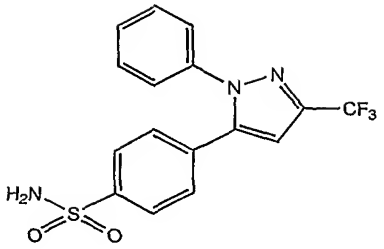
3-(4-fluorophenyl)-4-[4-(methylsulfonyl) phenyl]-2 (3H)-oxazolone;



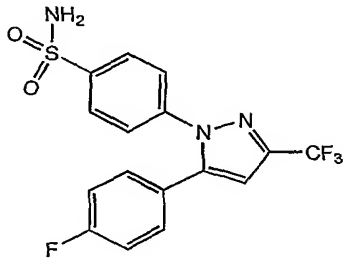
5-(4-fluorophenyl)-1-[4-(methylsulfonyl) phenyl]-3-(trifluoromethyl)-1H-pyrazole;



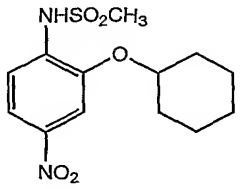
4-[5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl) benzenesulfonamide;



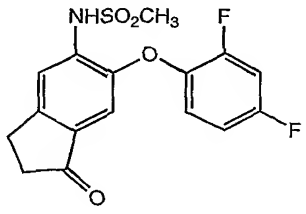
4-[1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl] benzenesulfonamide;



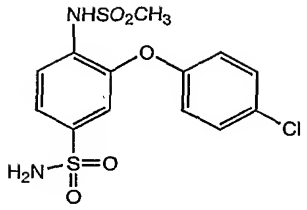
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;



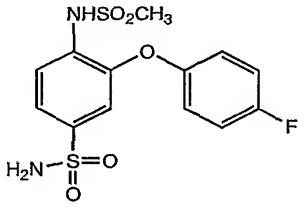
N-[2-(cyclohexyloxy)-4-nitrophenyl] methanesulfonamide;



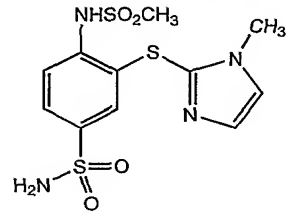
N-[6-(2, 4-difluorophenoxy)-2, 3-dihydro-1-oxo-1H-inden-5-yl] methanesulfonamide;



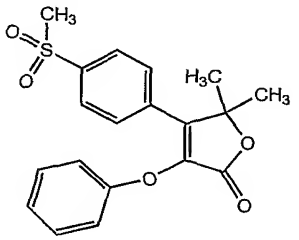
3-(4-chlorophenoxy)-4-[(methylsulfonyl) amino] benzenesulfonamide;



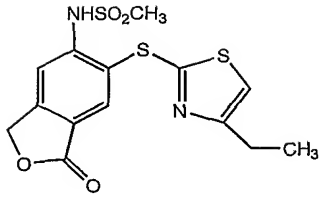
3-(4-fluorophenoxy)-4-[(methylsulfonyl) amino] benzenesulfonamide;



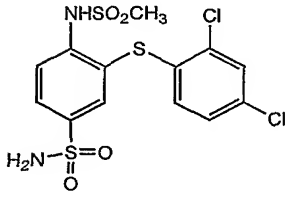
3-[(1-methyl-1H-imidzaol-2-yl)thio]-4 [(methylsulfonyl) amino] benzenesulfonamide



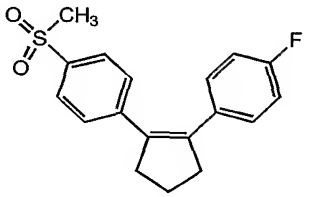
5, 5-dimethyl-4-[4-(methylsulfonyl) phenyl]-3-phenoxy-2(5H)-furanone;



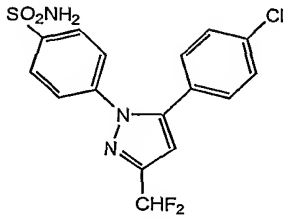
N-[6-[(4-ethyl-2-thiazolyl)thio]-1, 3-dihydro-1-oxo-5-isobenzofuranyl] methanesulfonamide;



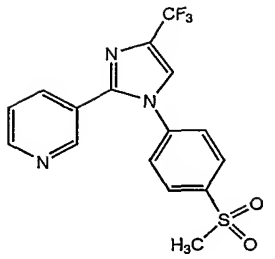
3-[(2, 4-dichlorophenyl)thio]-4-[(methylsulfonyl) amino] benzenesulfonamide;



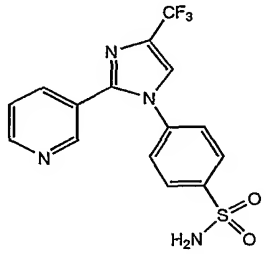
1-fluoro-4-[2-[4-(methylsulfonyl) phenyl] cyclopenten-1-yl] benzene;



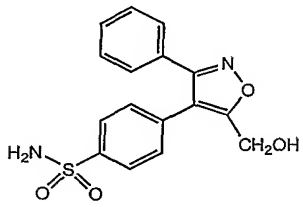
4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;



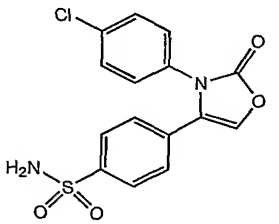
3-[1-[4-(methylsulfonyl) phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl] pyridine;



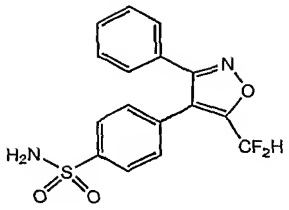
4-[2-(3-pyridinyll)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;



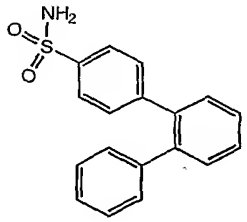
4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl] benzenesulfonamide;



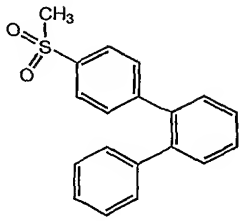
4-[3-(4-chlorophenyl)-2, 3-dihydro-2-oxo-4-oxazolyl] benzenesulfonamide;



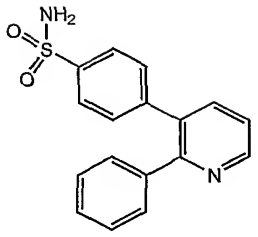
4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl] benzenesulfonamide;



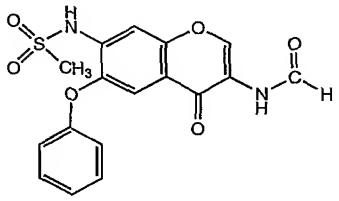
[1, 1':2', 1"-terphenyl]-4-sulfonamide;



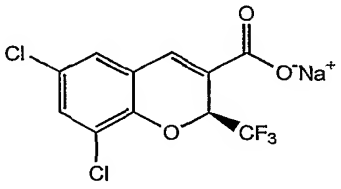
4-(methylsulfonyl)-1, 1', 2], 1"-terpheynyl;

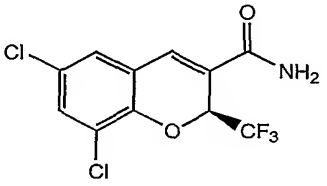


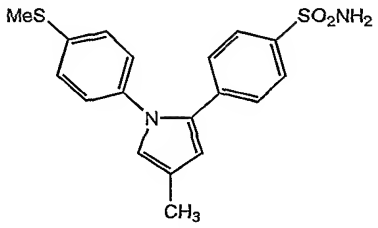
4-(2-phenyl-3-pyridinyl) benzenesulfonamide;

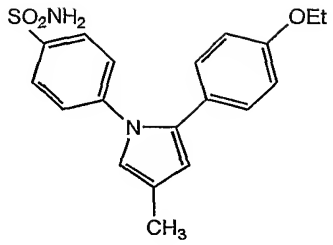


N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] methanesulfonamide;









compound T 614; darbufelone; compound L745337; celecoxib; compound CT3; rofecoxib; compound L783003; compound JT3 522; compound 754; parecoxib; compound S2474; compound LAS 33815; valdecoxib; and compound MK 663.

33. The method according to claim 29, wherein the COX-2 inhibitor is selected from the group consisting of celecoxib, rofecoxib, parecoxib and valdecoxib.

34. The method according to claim 29, wherein the COX-2 inhibitor is celecoxib.

35. The method according to claim 29, wherein the NSAID is selected from the group consisting of acetyl salicylic acid, indometacin, sulindac, phenylbutazone, diclofenac, fentiazac, ketorolac, piroxicam, tenoxicam, mecoxicam, meloxicam, cinnoxicam, ibufenac, ibuprofen, naproxen, ketoprofen, nabumetone, niflumic acid and nimesulide, or a pharmaceutically acceptable salt thereof.

36. The method according to claim 29, wherein the NSAID is selected from the group consisting of diclofenac, piroxicam, tenoxicam, mecoxicam, meloxicam, ibufenac, ibuprofen, naproxen and ketoprofen, or a pharmaceutically acceptable salt thereof.

37. The method according to claim 29, wherein the retinoid compound is selected from the group consisting of Accutane; Adapalene; AGN-193174; AGN-193676; AGN-193836; AGN-193109; AR-623; BMS-181162; CD-437; ER-34617; Etrinate; Fenretinide; Ligand LGD-1550; lexacalcitol; MX-781; mofarotene; MDI-101; MDI-301; MDI-403; Motretinide; 4-(2-[5-(4-methyl-7-ethylbenzofuran-2-yl)pyrrolyl])benzoic acid; N-[4-[2-thyl-1-(1H-imidazol-1-

yl)butyl]phenyl]-2-benzothiazolamine; Soriatane; SR-11262; Tocoretinate; Advanced Polymer Systems trans-retinoic acid; UAB-8; Tazorac; TopiCare; TAC-101; and Vesanoid.

38. The method according to claim 29, wherein the metallo-protease inhibitors is selected from the group consisting of:

1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

N-hydroxy-1-(pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-benzamide;

N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

BB-2516 (marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]- propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, [2S-[N4(R*), 2R*, 3S*]]-);

BMS 275291;

Bay-12-9566 (tanomastat), 4-[(4'-chloro[1,1-diphenyl]-4-yl)oxy]-2-[(phenylthio) methyl] butanoic acid;

AG-3340, N-hydroxy-2,2'-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-3-thiomorpholine-carboxamide;

CMT-3 (metastat), 6-demethyl-6-deoxy-4-dedimethylaminotetracycline, batimastat (BB-94); and

D-2163,2-[1S-([(2R,S)-acetylmercapto-5-phthalimido]pentanoyl-L-leucyl)amino-3-methylbutyl]imidazole.

39. The method according to claim 29, wherein the anti-estrogen is a SERM devoid of uterotrophic activity.

40. The method according to claim 29, wherein the SERM is selected from the group consisting of tamoxifen, toremifene, arzoxifene, idoxifene, EM 800, fulvestrant and droloxifene.

41. The method according to claim 29, wherein the GnRH agonist is selected from the group consisting of leuprorelin, deslorelin, triptorelin, buserelin, nafarelin, goserelin, avorelin, histerelin, compound PTL 03001, compound AN 207, compound TX 397, compound AN 201 and compound SPD 424, or a pharmaceutically acceptable salt thereof.

42. The method according to claim 29, wherein the GnRH agonist is selected from the group consisting of triptorelin, goserelin and leuprorelin or a pharmaceutically acceptable salt thereof.

43. The method according to claim 42, wherein the GnRH agonist is triptorelin pamoate.

44. The method according to claim 42, wherein the GnRH agonist triptorelin pamoate is in the form of a sustained release formulation, at a dosage from about 3 to about 20 mg.

45. The method according to claim 42, wherein the GnRH agonist triptorelin pamoate is in the form of 1 month depot formulation 3.75 mg.

46. The method according to claim 41, wherein exemestane and triptorelin or a pharmaceutically acceptable salt thereof are administered, and wherein hormone output of a patient's ovaries is inhibited and aromatase enzyme activity is inhibited or inactivated, whereby a therapeutically useful effect is achieved.

47. The method according to claim 29, wherein the GnRH antagonist is selected from the group consisting of cetrorelix, abarelix, ramorelix, teverelix, ganirelix, compounds A 75998 and A 84861, compound PM-OV-92, GnRH immunogen, compound D 26344, compound T 98475, and compound MI 1544, or a pharmaceutically acceptable salt thereof.

48. The method according to claim 29, wherein the GnRH antagonist is selected from the group consisting of cetrorelix, abarelix and ramorelix, or a pharmaceutically acceptable salt thereof.

49. The method according to claim 29, wherein the SPRM is dienogest or a pharmaceutically acceptable salt thereof.

50. The method according to claim 29, wherein the angiogenesis inhibitor is selected from the group consisting of an $\alpha v\beta 3$ integrin inhibitor, a protein kinase inhibitor, angiostatin, platelet factor 4 (endostatin), a VEGF inhibitor and thalidomide.

51. The method according to claim 29, wherein the angiogenesis inhibitor is thalidomide.

52. The method according to claim 50, wherein the $\alpha v\beta 3$ integrin inhibitor is selected from the group consisting of:

Vitaxin antibody (Ixsys); Merck KgaA EMD-121974, cyclo[RGDF-N(Me)V-];

(10S)-10,11-dihydro-3-[3-(2-pyridinylamino)propoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid;

(2S)-7-[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(2S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(5-methyl-1H-imidazo[4,5-b]pyridin-2yl]methyl]amino] carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(bR)-b-[[[(3R)-2-oxo-3-[2-(5,6,7,8-tetrahydro-[1,8]-naphthyridin-2-yl)ethyl]1-1-pyrrolidinyl] acetyl]amino]-d-(1H-indol-3-yl)pentanoic acid; and

(3R)-N-[3-hydroxy-5-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]-glycyl-3-(3-bromo-5-chloro-2-hydroxyphenyl)-b-alanine (compound SD 7784).

53. The method according to claim 50, wherein the protein kinase inhibitor is selected from compound SU6668 (3-[4-(2-carboxyethyl-3,5-dimethylpyrrol-2-yl)methylidenyl]-2-indolinone), and compound SU5416 (3-[(2,4-dimethylpyrrol-5-yl)methylidenyl]-2-indolinone).

54. The method according to claim 50, wherein the VEGF inhibitor is selected from the group consisting of compound SU 6668, compound SU 5416, rhuMAbVEGF and compound DC 101.